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Risk factors of Second Malignant Neoplasms in Childhood Cancer Survivors

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Abstract

Cancer is as the second leading cause of death among children in the United States. The mortality rate for cancer has witnessed a decline, dropping from 6.5 per 100,000 in 1970 to 2.3 per 100,000 in 2016. Second malignant neoplasms (SMNs) represent novel primary malignancies emerging after the initial cancer diagnosis, particularly prominent as late effects of cancer therapy in children. The incidence of SMNs sees a substantial increase over time, reaching nearly 10% even a decade after the initial diagnosis. A comparative analysis between the general population and child cancer survivors reveals a six-fold higher risk of developing SMNs among the latter. Various factors contribute to the elevated risk of second cancers, with age, lifestyle, environmental influences, primary cancer treatment, and genetic predisposition playing pivotal roles. Noteworthy risk factors for SMNs in children encompass radiation therapy, chemotherapeutic agents, topoisomerase inhibitors, genetic factors, hematopoietic stem cell transplantation, and ionizing radiation, as elucidated in the present study. Despite these findings, further research is imperative to accurately quantify the risks associated with etiological factors, enabling the identification of individuals at a heightened risk for second cancers and facilitating proactive screening and preventive measures.

Keywords: Cancer, Children, Risk factors, Second Malignant Neoplasms

Introduction

Cancer is the second leading cause of death in children in the United States (1-4). The mortality rate for cancer in children has seen a noteworthy decrease, dropping from 6.5 per 100,000 in 1970 to 2.3 per 100,000 in 2016, marking a reduction of almost 65% and 61% for children and adolescents, respectively (1-3). The survival rate after pediatric cancer in both the United States and Europe exceeds 80% (5, 6). However, as the survival rates for children with cancer improve, the long-term effects of treatment become more pronounced, adding to the overall burden (1).

Leukemia, brain and spinal cord tumors, neuroblastoma, Wilms' tumor, lymphoma (including both Hodgkin and non-Hodgkin), rhabdomyosarcoma, retinoblastoma, and bone cancer (including osteosarcoma and Ewing sarcoma) are the most prevalent types of cancer in children. While other types of childhood cancers are rare, they do occur on occasion (7). Advances in early detection, supportive care, and treatment have contributed to an increased number of cancer survivors, with a 5-year survival rate of approximately 66.1% (8).

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The growing population of childhood cancer survivors has, in turn, led to a significant rise in the incidence of second malignant neoplasms (SMNs) following childhood cancer (9, 10). The occurrence of SMNs in childhood cancer survivors not only diminishes their life expectancy but also impairs their overall quality of life (9, 11). Notably, children who are cancer survivors tend to have a longer life expectancy compared to adult cancer survivors (9, 11).

Childhood Cancer

Childhood cancer affects individuals between birth and 14 years of age (12). In the United States, it stands as the second leading cause of death among children under 14 years, following unintentional injuries (12, 13). The incidence of childhood cancer in children under 15 years is approximately 140 per million. Studies indicate a consistent increase in the occurrence of cancer among children in developed countries since the 1950s (14). The predominant form of cancer in children is leukemia, typically manifesting before the age of 20. There are two primary types of childhood leukemia: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Among these, acute lymphoblastic leukemia (ALL) is the most common (3). The incidence peak for ALL is observed between 2-5 years old. Furthermore, the survival rate for children diagnosed with ALL is nearly 90% (3).

Furthermore, there has been a 0.8% annual increase in the incidence ALL from 1975 to 2006. The second-largest category of neoplasms among children is central nervous system (CNS) tumors, constituting 17% of childhood cancers. Among CNS cancers, over half are represented by a specific type of brain tumor called astrocytomas. Lymphomas and other reticuloendothelial neoplasms contribute to 16% of childhood cancers, while melanoma and thyroid cancer make up 9%. Germ cell, trophoblastic, and other gonadal neoplasms account for 7% of childhood cancers. Following closely are soft tissue sarcomas, malignant bone tumors, sympathetic and allied nervous system tumors, renal tumors, retinoblastoma, and hepatic tumors (15).

Second malignant neoplasms (SMNs)

Second malignant neoplasms (SMNs) refer to new primary malignancies arising after the diagnosis of an initial cancer, representing a significant late effect of cancer therapy in children (16). Among long-term survivors of childhood cancer, SMNs constitute a substantial and critical cause of mortality (17). Over time, the incidence of SMNs increases significantly, reaching nearly 10% even a decade after the initial diagnosis (18, 19). A comparison between the development of the first cancer in the general population and in childhood cancer survivors reveals a six-fold higher risk of developing SMNs among the latter (20-22).

According to research findings, among individuals who have survived cancer for 25 years, second malignant neoplasms (SMNs) result in more fatalities than any other cause (20, 23). Yavari et al., demonstrated that SMNs contribute to approximately half of non-relapse deaths among survivors of primary cancer after five years (1). Children and adolescents who have survived Hodgkin's lymphoma are particularly susceptible to developing various second malignant neoplasms, such as those affecting the thyroid, gastrointestinal system, lungs, leukemia, sarcomas, and breast carcinoma (24).

The risk of developing second cancers in adults varies significantly based on factors like age, the presence of second cancer risk factors such as lifestyle and environmental influences, primary cancer treatment, and genetic predisposition (11). Common

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second malignancies observed in pediatric cancer survivors include breast and thyroid carcinoma, nonmelanoma skin cancer, bone tumors, and benign central nervous system tumors like meningiomas.

Osteosarcoma (as a second primary malignant neoplasm)

Osteosarcoma serves as a subsequent primary malignant neoplasm and frequently arises as a result of prior cancer therapy or genetic predisposition (25). It stands out as the most prevalent secondary malignancy occurring within the initial two decades following a childhood cancer diagnosis. Increased susceptibility to osteosarcoma is linked to a history of retinoblastoma, Paget's disease of the bone, Rothmund–Thompson syndrome, Ewing's sarcoma, and Li–Fraumeni syndrome (25). Specific genetic abnormalities associated with the development of osteosarcoma have been identified in cases of retinoblastoma. Additionally, the exposure to anthracyclines, alkylating agents, and radiation therapy has been observed in the onset of secondary osteosarcoma.

The risk factors for SMNs include

The most crucial risk factors for SMNs are presented as follows.

Chemotherapeutic agents

Alkylating agents, including ifosfamide, mechlorethamine, cyclophosphamide, melphalan, busulfan, cisplatin, dacarbazine, and nitrosoureas, are commonly employed in current therapies for solid tumors, hematologic malignancies, and preconditioning regimens for hematopoietic stem cell transplantation (HSCT). However, the use of alkylating agents is a significant risk factor for the development of second malignant neoplasms (SMNs), leading to an increased relative risk (RR) for SMNs. Exposure to alkylating agents is notably associated with an elevated risk of hematologic malignancies, such as treatment-related acute myelogenous leukemia (t-AML) (26).

It appears that t-AML resulting from the use of alkylating agents exhibits specific characteristics (26). Alkylating agents are commonly employed in the treatment of Hodgkin's lymphoma, and patients undergoing such treatment have an increased risk of developing t-AML. Numerous studies have also highlighted a noteworthy rise in the incidence of t-AML in individuals with Hodgkin's lymphoma treated with MOPP (26, 27).

Topoisomerase inhibitors

Additional chemotherapeutic agents utilized in the treatment of pediatric cancers include Topoisomerase II inhibitors, comprising anthracyclines, anthracenediones (such as mitoxantrone), and epipodophyllotoxins like etoposide and teniposide. In the late 1980s, Rastin and colleagues confirmed that treatment-induced acute myelogenous leukemias (t-AMLs) caused by Topoisomerase II inhibitors are widely acknowledged, with an incidence reaching up to 8.3%. A comprehension of the mechanism through which topoisomerase II hinders DNA cleavage sites has contributed to the clarification of its leukemogenic characteristics. Specifically, a model has shown that incorrect repair of DNA cleavage sites following topoisomerase II inhibition leads to characteristic translocations, which have become the hallmark of t-AML (28).

Research indicates that t-AML resulting from Topoisomerase II inhibitors and epipodophyllotoxins exhibits various distinctive cytogenetic features (26). The most commonly observed translocation in t-AML involves the MLL gene at 11q23. Since the initial report by Pedersen-Bjergaard et al. in 1998, the 11q23 translocation is now observed in t-AML resulting from epipodophyllotoxins (26).

After the administration of various combinations of Topoisomerase II

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inhibitors, the t(8;21)(q22;q22) translocation is often observed, resulting in the fusion AML1-ETO gene product (RUNX1-RUNX1T1) associated with French-American-British (FAB) M2 AML (26). Furthermore, the use of anthracyclines is linked to the t(8;16)(p11;p13.3) translocation, a rare occurrence in t-AML (26).

Genetic factor

The polymorphisms of thiopurine methyltransferase, as one of the metabolizing genes of 6-mercaptopurine (6-MP) are a potential risk factors for SMNs, because of the increasing DNA damaging effect of 6-MP during acute lymphoblastic leukemia (ALL) therapy in patients with low activity of thiopurine methyltransferase (29, 30). The mechanism which 6-MP induces SMNs remains unclear. In addition, polymorphisms of thiopurine methyltransferase are rare in individuals of East Asia. The polymorphisms of another 6-MP–metabolizing gene, such as nucleoside diphosphate–linked moiety X-type motif 15 are common (29, 31, 32), but there are no reports regarding an association between nucleoside diphosphate–linked moiety X-type motif 15 and SMNs.

Role of ionizing radiation

Ionizing radiation (IR) serves as the conventional approach for managing various pediatric malignancies, encompassing CNS malignancies, solid tumors, and Hodgkin's lymphoma (HL). However, IR also emerges as a prominent therapeutic method for treating several primary CNS malignancies, thereby posing a substantial challenge in terms of secondary malignant neoplasms (SMNs) (26).

The literature underscores the role of IR as a carcinogen and delineates the associated risk of developing SMNs. Additionally; IR exposure is correlated with a relative risk for SMN development, emerging as a robust independent risk factor. Patients who undergo radiation therapy exhibit a significantly higher incidence of SMNs compared to those who do not. Moreover, radiation therapy targeting the CNS is linked to an elevated risk of brain tumors, particularly gliomas, including secondary malignant gliomas.

Role of hematopoietic stem cell transplantation (HSCT)

Hematopoietic stem cell transplantation (HSCT) is a therapeutic approach for pediatric cancer treatment, but it is associated with an eight-fold higher incidence of secondary malignant neoplasms (SMNs) compared to the general population. Various factors related to HSCT, such as the choice of chemotherapy conditioning regimen, graft-versus-host disease, and the use of pretransplant radiation; contribute to the heightened risk of SMNs in survivors of pediatric cancer (26).

It is suggested that individuals who undergo HSCT face an increased risk of treatment-related acute myelogenous leukemia/myelodysplastic syndrome (t-AML/MDS) due to exposure to specific chemotherapeutic agents during the preconditioning phase (26). According to one study, secondary osteosarcomas originating from HSCT recipients often manifest in locations other than the extremities, accounting for 59.8% of cases compared to primary osteosarcomas at 24.8%. Moreover, studies suggest that secondary osteosarcomas are more commonly linked to an advanced age demographic, with 48.8% occurring in individuals aged 60 and above. The majority of these secondary osteosarcomas (66.7%) are observed subsequent to primary carcinomas at diverse anatomical locations.

Radiotherapy

Cancers triggered by radiation have been recognized. Despite advancements, there's a growing concern about an elevated risk

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of second cancers in long-term survivors. The primary risk factor for secondary thyroid carcinoma in survivors of childhood cancer is radiotherapy targeting the thyroid gland. Its impact appears to be influenced by a sigmoidal dose–response relationship (4). In addition, various radiotherapy treatments administered to individuals with Hodgkin's lymphoma contribute to the development of secondary cancers. Employing radiotherapy at a younger age is linked to an increased likelihood of secondary cancer. Based on the analysis of multiple articles, solid tumors tend to emerge, on average, 10-12 years after undergoing radiotherapy for Hodgkin's lymphoma treatment (3). Table I shows evaluation of second malignant neoplasms in children.

Table I: Evaluation of second malignant neoplasms in children

Researcher	Explanation	Results
Meadows, 1985 (33)	This study assessed SMNs in children	Bone sarcoma emerged as the most prevalent secondary malignancy.
Tarbell, 1993 (34)	This research examined how gender disparities influence the likelihood of second malignant tumors following childhood Hodgkin's disease.	The cumulative occurrence of second cancers raises a decade post-treatment.
Rich ,1997 (35)	`These researcher evaluated the second malignant neoplasms in children	The primary secondary malignancy observed was bone sarcoma (6 out of 20 cases), succeeded by brain tumors (3 cases), leukemia (2 cases), and other types of sarcomas.
Garwicz, 2000 (36)	They evaluated SMNs in childhood and adolescence.	The most significant treatment-related risk factor for the onset of secondary malignant neoplasms (SMN) was radiation.
Neglia, 2001 (37)	This study evaluated the SMNs in childhood cancer.	Twenty years after diagnosis of cancer in children, the SMNs incidence in children was 3.2 %. Moreover, SMNs of any type were independently associated with childhood Hodgkin's disease or soft-tissue sarcoma, and exposure to alkylating agents.
Le Deley , 2003 (38)	They assessed the risk of secondary leukemia after a solid tumor in children using epipodophyllotoxins (1.2 and 6 g/m^2) and anthracyclines (more than 170 mg/m^2)	Both epipodophyllotoxins and anthracyclines increased the risk of secondary leukemia.
Jenkinson, 2004 (39)	This study evaluated SMNs after childhood cancer in Britain.	Among 16451 survivors of childhood cancer after 3 years, 278 cases of SMNs were identified.
Kevin C., 2006 (40)	Long-term health issues in individuals who survived childhood cancer.	The mean age of patients was 26.6 years**.** Survivors of children with cancer during childhood have a high rate of illness owing to chronic health conditions.

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Debra L. Friedman, 2010 (41)	Occurrences of new tumors in individuals who survived childhood cancer for at least five years: findings from the Childhood Cancer Survivor Study.	The survivors of childhood cancer progress through adulthood and patients surviving Hodgkin lymphoma are at greatest risk.
Tukenova, 2010 (42)	This study evaluated long-term mortality of SMNS in 5-Year survivors of solid childhood tumors.	5-year survivor of cancer in children is associated with a high long-term mortality risk for SMNS.
Castellino, 2011 (43)	Health issues and death rates among individuals who have survived Hodgkin lymphoma in the long term.	Elevated death rates from subsequent neoplasms and cardiovascular disease show variations based on gender and endure for more than two decades of monitoring in survivors of childhood Hodgkin lymphoma.
Kumar, 2012 (44)	This research assessed the occurrence of secondar malignant neoplasms subsequent to radiotherapy.	This risk of SMNs appears to be highest for survivors of childhood cancers after radiation therapy.
Tukenova, 2012 (45)	They evaluated SMNs after childhood cancer.	Childhood cancer therapy strongly enhances the risk of SMDO after a very long latency period.
Braam, 2012 (46)	They examined malignant melanoma as a secondary malignant neoplasm in individuals who had survived childhood cancer over the long term.	Risk factors associated with malignant melanoma as a secondary malignant neoplasm included exposure to radiotherapy or a combination of alkylating agents and anti-mitotic drugs.
Armstrong, 2013 (47)	They examined significant cardiac events in adults who had survived childhood cancer	Cardiovascular risk factors, such as hypertension, amplify the therapy-related risk of major cardiac events in this particular population.
Schmiegelow, 2013 (48)	They evaluated second malignant neoplasms after treatment of childhood ALL.	SMNs after diagnosis of childhood ALL are rare events.
Ward, 2014 (49)	They evaluated childhood cancer in children	Malignant CNS tumors are the second most common cancer in children.
Young Ju H, 2018 (50)	They assessed the SMNs after childhood cancer in Korea.	Cancer survivors had 20-fold higher risk for developing a malignant neoplasm than general population.
Moser, 2021 (51)	This research examined the occurrence of secondary malignancies following the treatment of non-Hodgkin lymphoma in childhood.	In the first, 3590 patients were diagnosed with cancer. After follow-up of 9.4 years, 95 second malignant neoplasms. A total of 26 carcinomas were identified, comprising 9 basal cell carcinomas, 21 cases of acute myeloid leukemias/myelodysplastic syndromes, 20 lymphoid malignancies, 12 central nervous system tumors, and 16 others.
Ho, 2022 (52)	Characteristics and results of second malignancies in individuals with a history of childhood cancer.	For those diagnosed with a second cancer, the risk of mortality is heightened when the primary diagnosis occurred on or before 2002, the age at the second cancer diagnosis is 9.3 years or younger, and if the second cancer is a hematological malignancy. This suggests that children facing a second cancer encounter an unfavorable prognosis.

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Conclusion

The risk of second cancers in adults varies significantly based on factors such as age, the prevalence of second cancer risk factors, including lifestyle and environmental influences, the primary cancer therapy received, and genetic susceptibility. In children, identified risk factors for second malignant neoplasms encompass radiation therapy, chemotherapeutic agents, topoisomerase inhibitors, genetic factors, hematopoietic stem cell transplantation, and ionizing radiation, all of which are discussed in the present study. Nevertheless, further research is needed to quantify the risks associated with etiological factors and to identify individuals at a heightened risk of developing a second cancer, facilitating screening and preventive efforts.

Conflict of interest

None

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